REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following remarks.

I. Status of the claims

Claims 175-210 are currently pending in the application, with claim 175 being the independent claim. Claims 1-174 were previously cancelled without prejudice to or disclaimer of the subject matter therein. Claims 180-199 are withdrawn from consideration pursuant to an Election of Species Requirement. Thus, claims 175-179 and 200-210 are currently under examination.

II. The Amendment to the Claims

Claim 175 is amended to specify that the claimed method is for determining the Braak stage of neurofibrillary degeneration associated with tauopathy, and may be used for the detection of early Braak stages before appearance of clinical symptoms, pre-mortem diagnosis or discrimination of advanced Braak staging. Support for the amendments to claim 175 may be found, *inter alia*, throughout the specification and in particular at page 3 of the published patent application, paragraph [0039].

Claim 178 is amended to clarify that the extent of neurofibrillary degeneration is related to the Braak neuropathological staging of Alzheimer Disease progression. Support for the amendments to claim 178 may be found, *inter alia*, at pages 3-4 of the published patent application, paragraphs [0039] and [0072].

Claim 202 is amended to eliminate reference to Figure 8b and recite the compounds listed in the figure. Support for the amendment to claim 202 may be found, *inter alia*, in Figure 8b as originally filed.

Claim 206 is amended to specify that the blocking ligand labels competing non-aggregated tau binding sites present in the medial temporal lobe and in the neocortical structure of the brain. Support for the amendment to claim 206 may be found, *inter alia*, at page 4 of the published patent application, paragraphs [0057] and [0062].

Claim 207 is amended to replace the term "phenylene" with the term "phenyl". Support for the amendment to claim 206 may be found, *inter alia*, in the benzothiazole compound represented by the formula depicted in paragraph [0229] of the published patent application.

Finally, claims 175, 179, 201, 206, 207, 209 and 210 are amended to correct formal matter.

These amendments do not introduce any new matter into the application and their entry is respectfully requested.

III. The Personal Interview with the Examiner

Applicants thank Examiners Jagadishwar Rao Samala and Blessing Fubara for the courtesy extended to Applicants and Applicants' representative in the personal interview held on June 14, 2007. The claims presented herein and the following remarks reflect the issues discussed and agreed upon during the interview.

IV. The Election Requirement

The Office Action, at page 2, makes the election of species requirement final and withdraws claims 180-199 from consideration. Applicants reserve the right to have the non-elected species examined when the elected claims are allowed (including any claims depending from the allowed generic claim), and further to file one or more divisional applications covering the subject matter of the non-elected species, as appropriate.

V. The Objection to the Claims

The Office Action, at page 2, objects to claim 202 for referring to Figure 8b. Claim 202 is amended to eliminate reference to Figure 8b and recite the compounds listed in the figure. Accordingly, the objection is moot. Reconsideration and withdrawal of this ground of objection is therefore respectfully requested.

VI. The Rejection Under 35 U.S.C. § 112, First Paragraph

The Office Action, at pages 2-3, rejects claim 207 under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not enable the person skilled in the art o which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with the claimed invention.

Specifically, the Office Action asserts that "[i]n the instant claimed blocking ligand, the mode of attachment or linkage of one of the phenylene substituent to the benzene ring carrying the NR2 group is not clearly understood." Further, the Office Action alleges that since the invention is concerned with a wide range of blocking ligands, the artisan skilled in the art would need undue experimentation to practice the invention, and concludes that the specification is not sufficient to support the claims. Applicants respectfully traverse this ground of rejection.

The MPEP § 2164.08 states the following with regard to enablement commensurate in scope with the claims:

> The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without `undue experimentation'." *In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)*. Nevertheless, not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. *In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991)*. All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of

> knowledge and skill in the art. Further the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. *See, e.g., In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).*

With regard to the breadth of a claim, the MPEP states:

> As concerns the breadth of a claim relevant to enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. *In re Moore, 439 F.2d 1232, 1236, 169 USPQ 236, 239 (CCPA 1971).*

The M.P.E.P. § 2164.01 additionally notes: "*The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.*".

Furthermore, the Federal Circuit has recently clarified the law regarding written description in *Faulkner-Gunter Falkner v. Inglis*, 448 F.3d 1357 (Fed. Cir. 2006). Specifically, the court has favorably cited *LizardTech Inc. v. Earth Resource Mapping, PTY Inc.*, 424, F.3d 1336 (Fed. Cir. 2005), explaining that the specification is written for a person skilled in the art and it is unnecessary to spell out every detail of the invention, only enough is required to convince a person of skill in the art that the inventor possessed the invention and to enable the person to make and use the invention without undue experimentation. *Id.*

In the current application, Applicants have sufficiently disclosed the invention to meet the written description requirement in line with the reasoning provided by the Federal Circuit, and to enable the person skilled in the art to make and/or use the invention according to the M.P.E.P. guidelines. In fact, the specification (*see* paragraphs [0057]-[0060] in the published patent application), states the following:

> In one embodiment of the invention, steps (i) and/or (ii) of the method are performed in conjunction with (preferably preceded by) the further step of introducing into the subject a second ligand

> which labels competing (i.e. non-aggregated tau) binding sites present in the relevant region of the brain preferentially to the first ligand.
>
> Thus the methods and other embodiments herein may include a step: (ibis) introducing into the subject a blocking ligand which labels non-aggregated tau binding sites in the brain of the subject preferentially to the ligand capable of labelling aggregated PHF tau.
>
> A competing binding site may be one which is provided by e.g. amyloid plaques, such as may be present in the subject. By introducing such second ligands into the subject, the relative or effective concentration of first ligand available to bind to aggregated tau may be enhanced. Suitable second ligands (or blocking compounds as they may be described herein) are described below, but they may in particular include benzothiazoles such as are shown in FIG. 5, compounds 1B and 2. Another suitable blocking ligand may be FDDNP of Shoghi-Jadid *et al., Am. J. Geriatr. Psychiatr. 2002, 10*:24-35, discussed above.

Furthermore, Applicants have taken into consideration the concern expressed by the Examiner during the interview. The Examiner requested clarification with regard to the phrase "phenylene group", alleging that the phenylene is described in the specification as a C_1-C_4 alkyl. Thus, solely to advance prosecution, and not in acquiescence with the propriety of the rejection, the foregoing amends claims 207 to replace the term "phenylene" with the term "phenyl", as suggested by the Examiner.

The variable $R^p{}_m$ is drawn in the structure of the blocking ligand. Based on the description, it is evident that R^p attaches to the phenyl ring through a covalent bond. As described on page 33, lines 28-29 of the application, examples of phenylene substituents R^p include, but are not limited to, C_{1-4} alkyl groups. Exemplary blocking ligands are depicted in FIG. 5 as compounds 1b and 2, wherein each of the R^p is H. *See* paragraph [0253] at page 12 of the published patent application.

The blocking ligand used in the present invention is either [^{18}F]FDDNP or a benzothiazole. These ligands can be synthesized by one of ordinary skilled in the art without undue experimentation using methods known in the art, such as those illustrated in U.S. Patent No. 5,371,232 and U.S. Patent No. 5,008,009. The '232 patent describes the preparation of 2-(4-aminophenyl) benzothiazole compounds and the '009 patent describes diazotization of 2-(4-aminophenyl) benzothiazole compounds (*see* col. 11, lines 17-37).

Thus, the artisan skilled in the art, reading the specification, can readily identify, produce and use the claimed blocking ligands using the techniques known in the art or described in the specification. Accordingly, the specification provides a complete description of the invention and full enablement commensurate in scope with the claimed invention. Reconsideration and withdrawal of this ground of rejection is therefore respectfully requested.

VII. The Rejection Under 35 U.S.C. §102(b)

The Office Action, at pages 3-4, rejects claims 175-179 under 35 U.S.C. §102(b) as allegedly anticipated by WO96/30766 to Wischik *et al.* ("Wischik I"). Specifically, the Office Action alleges that Wischik I discloses methods for the detection of substances capable of modulating or inhibiting pathological tau-tau protein association and aggregation, methods for the screening of therapeutic agents, and the use of phenothiazine compounds for the treatment of Alzheimer's Disease. Applicants respectfully traverse this ground of rejection.

A. Summary of the Claimed Invention

The presently claimed invention is directed to a method for determining the *Braak stage* of neurofibrillary degeneration associated with a tauopathy in a subject believed to suffer from the disease comprising the steps of: (i) introducing into the subject a *ligand conjugated, chelated, or associated with a detectable chemical group*, that labels aggregated paired helical filament (PHF) tau protein and is capable of crossing the blood brain barrier; (ii) determining the presence and\or amount of ligand bound to extracellular aggregated PHF tau in the *medial*

temporal lobe of the brain of the subject; and (iii) correlating the results of the determination with the extent of neurofibrillary degeneration in the subject. The method may be used for the detection of early Braak stages before appearance of clinical symptoms, pre-mortem diagnosis and discrimination of advanced Braak staging and may be practiced *in vivo*, *in vitro* and *ex vivo*.

Tauopathies are neurodegenerative disorders characterized by abnormal tau aggregation. As stated in the specification (*see* paragraph [0305] in the published patent application), exemplary tauopathies include Alzheimer's Disease, Pick's disease, Progressive Supranuclear Palsy (PSP), fronto-temporal dementia (FTD), parkinsonism linked to chromosome 17 (FTDP-17), disinhibition-dementia-parkinsonism-amyotrophy complex (DDPAC), pallido-ponto-nigral degeneration (PPND), Guam-ALS syndrome, pallido-nigro-luysian degeneration (PNLD), cortico-basal degeneration (CBD), as well as others.

There is a critical need in the art for non-invasive methods of detection of tauopathies, such as Alzheimer's Disease, at an early stage. Early diagnosis is crucial for effective treatment. This invention provides a method to specifically assess neuropathological Braak staging in the medial temporal lobe of the brain and determine whether a subject is susceptible to tauopathy even before clinical symptoms are detected. As stated in the specification, in the course of development of tauopathy, paired helical filaments (PHFs), after assembling as filaments within the cytoplasm, form intracellular neurofibrillary tangles (NFTs). This process is exponential and eventually leads to functional impairment of neurone cells and cell death, with accumulation of extracellular NFTs. Thus, the assessment of extracellular neurofibrillary tangles in selected regions of the brain is critical, as it measures cell death and determines Braak staging.

Moreover, the method can be used to detect and asses later stages of the tauopathy in the neocortical regions of the brain and may be practiced pre-mortem and post-mortem.

As demonstrated in Example 1 and Figures 25-30, the present inventors have surprisingly devised a method to measure extracellular deposits of PHF-tau in patients *in vivo* using

conjugated ligands in medial temporal lobe structures and correlate the findings to Braak staging of neurofibrillary degeneration.

B. The Cited Reference Fails to Teach Each and Every Element of the Claimed Invention

Wischik I discloses methods for the detection of substances capable of modulating or inhibiting pathological tau-tau protein association and pathological neurofilament aggregation, with the purpose of identifying prophylactic and therapeutic agents for the treatment of Alzheimer's disease (*see* page 1, lines 1-8). Specifically, Wischik I describes an *in vitro* method for the identification of modulators or inhibitors of pathological tau-tau aggregation, that comprises contacting a first tau protein containing the tau core fragment with a possible modulator or inhibitor of tau-tau association and with a second labeled tau protein capable of binding the first tau protein, and detecting tau-tau binding (see page 8, lines 13-25).

Wischik I fails to teach or suggest several essential elements of the claimed invention. **First**, Wischik I fails to teach or suggest a method for determining the Braak stage of neurofibrillary degeneration associated with a tauopathy. Instead, Wischik I is concerned with the identification of possible therapeutic or prophylactic agents for the treatment of Alzheimer's Disease, and makes no mention of a diagnostic method for determining staging of the disease in a patient.

Second, Wischik I fails to disclose or suggest a ligand conjugated, chelated, or associated with a detectable chemical group, that labels aggregated paired helical filament (PHF) tau protein and is capable of crossing the blood brain barrier. In fact, although Wischik I discloses phenothiazines as inhibitors of tau-tau aggregation (*see* pages 25-31), the reference teaches that these compounds could be used as medicaments after further testing for toxicity (*see* page 29, lines 15-19), and fails to teach or suggest conjugating, chelating or associating these compounds, let alone using these compounds to label PHFs.

Third, Wischik I fails to disclose or suggest determining the presence and\or amount of ligand bound to extracellular aggregated PHF tau in the *medial temporal lobe of the brain* of the subject. Rather, Wischik I teaches that PHF tau fragment and soluble tau protein are isolated from whole brain tissues (*see* page 12, lines 14-37). Access to different sections of the brain is critical for diagnostic determination of disease progress and staging. Figure 2b in the specification shows the neuropathological staging of Braak in the different sections of the brain. Figures 25-27 in the disclosure, for example, show the probability of extracellular and intracellular tangles as a function of Braak staging in different regions of the brain and how the method of the invention allows earlier detection of the disease. As stated in the specification (*see* Example 1 and legend of Figure 26), intracellular tangles are not particularly helpful at detecting early Braak stages in the medial temporal lobe of the brain, but can detect later Braak stages in neocortical regions. In contrast, total brain extracts, such as the ones disclosed in Wischik I, are not diagnostic and thus cannot be used in the method of the present invention.

Fourth, Wischik I discloses an *in vitro* screening method, using neuronal cell lines (*see* Examples), and thus fails to teach or suggest a method that is practiced in patients *in vivo* to determine whether a subject is affected by or is susceptible to a tauopathy even before clinical symptoms are detected, and can be used *in vitro* and *ex vivo* as well.

Essentially, Wischik I is silent about pre-mortem detection, diagnosis and Braak staging of tauopathies by conjugated, chelated or detectable chemical group-associated ligands, let alone specifically in the medial temporal lobe of the brain.

Accordingly, at least for all the reasons stated above, Wischik I fails to anticipate the claimed invention. Reconsideration and withdrawal of this ground of rejection are therefore respectfully requested.

VIII. The Rejection Under 35 U.S.C. § 103

The Office Action, at pages 5-6, rejects claims 175-179 and 200-210 as being allegedly unpatentable over Friedhoff *et al. Biochemistry 37*: 10223-10230 (1998) ("Friedhoff") in view of Wischik *et al. Proc. Natl. Acad. Sci. 93*: 11213-11218 (1996) ("Wischik II") and U. S. Patent No. 5,008,099 to Quay *et al.* ("Quay"). Applicants respectfully traverse this ground of rejection.

The Supreme Court recently reaffirmed the Graham factors for determining obviousness in *KSR Int'l Co. v. Teleflex Inc.* (No. 04-1350) (U.S., April 30, 2007). The Graham factors, as outlined by the Supreme Court in *Graham et al. v. John Deere Co. of Kansas City et al.*, 383 U.S. 1 (1966), are: 1) determining the scope and contents of the prior art; 2) ascertaining the differences between the claimed invention and the prior art; 3) resolving the level of ordinary skill in the pertinent art; and 4) evaluating evidence of secondary consideration. The Supreme Court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a), and held that the proper inquiry for determining obviousness is whether the improvement is more than the predictable use of prior art elements according to their established functions. The Court noted that it is "*important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements" in the manner claimed*, and specifically stated:

> Often, it will be necessary . . . to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was ***an apparent reason to combine the known elements in the fashion claimed*** by the patent at issue. To facilitate review, this analysis should be made explicit.

KSR Int'l Co. v. Teleflex Inc., slip op. at 14 (emphasis added).

As discussed below, the differences between the prior art and the present application are so substantial, that the cited art cannot render the claimed invention obvious.

A. Summary of the Claimed Invention

As stated above, the presently claimed invention is directed to a method for determining the *Braak stage* of neurofibrillary degeneration associated with a tauopathy in a subject believed to suffer from the disease comprising the steps of: (i) introducing into the subject a *ligand conjugated, chelated, or associated with a detectable chemical group*, that labels aggregated paired helical filament (PHF) tau protein and is capable of crossing the blood brain barrier; (ii) determining the presence and\or amount of ligand bound to extracellular aggregated PHF tau in the *medial temporal lobe of the brain* of the subject; and (iii) correlating the results of the determination with the extent of neurofibrillary degeneration in the subject. The ligand is a phenothiazine, and specifically methylene blue. The method may be used for the detection of early Braak stages before appearance of clinical symptoms, pre-mortem diagnosis and discrimination of advanced Braak staging and may be practiced *in vivo*, *in vitro* and *ex vivo*.

The method of the invention may further include the use of a different ligand to bind intracellular aggregated PHF tau in a neocortical region of the brain.

Finally, the method of the invention encompasses the use of a ***blocking ligand*** to label *competing non-aggregated tau binding sites* in the medial temporal lobe and in the neocortical region of the brain **in addition to** the conjugated, chelated or associated with a detectable chemical group ligand that labels aggregated paired helical filament (PHF) tau protein described above. The blocking ligand according to the invention is either [^{18}F]FDDNP or a benzothiazole.

B. The Cited References Fail to Teach Each and Every Element of the Claimed Invention

The primary reference, Friedhoff, discloses an assay to monitor *in vitro* PHF assembly from tau protein in real time using thioflavine dyes, specifically thioflavin S (ThS) and thioflavin T (ThT), to stain amyloid-like deposits and neurofibrillary tangles in post-mortem brains.

Friedhoff fails to teach or suggest several elements of the claimed invention.

First, Friedhoff neither teaches nor suggests a method for determining the Braak staging of neurofibrillary degeneration associated with a tauopathy *in vivo* in a patient. Rather, Friedhoff discloses an *in vitro* assay that uses post-mortem brains (*see* pages 10223 and 10225).

Second, Friedhoff fails to disclose or suggest a *ligand conjugated, chelated, or associated with a detectable chemical group,* and specifically conjugated, chelated or detectable chemical group-associated methylene blue, that labels aggregated paired helical filament (PHF) tau protein and is capable of crossing the blood brain barrier. Instead, Friedhoff discloses thioflavins compounds, specifically ThS and ThT, that are not conjugated, chelated or associated with a detectable chemical group.

Third, Friedhoff fails to teach or suggest a ligand that selectively binds to extracellular aggregated PHF tau in the medial temporal lobe of the brain of a patient. The thioflavine S and thioflavine-T disclosed by Friedhoff are standard fluorescent stains that bind to amyloid protein deposits and are commonly used in neuropathological studies of AD. As stated in the specification (*see* paragraph [0052] in the published patent application), during the process of aggregation, tau protein acquires binding sites for compounds such as thiazin red and thioflavin-S. These histological markers label both intracellular and extracellular tangles and thus fail to differentiate between extracellular and intracellular binding sites. As demonstrated above, this distinction between extracellular and intracellular tangles is crucial to assess the Braak staging of the tauopathy. Friedhoff, however, makes no mention of it.

Furthermore, Example 2 in the specification shows that thioflavin-T is not effective in labeling tangles, and Example 5 demonstrates that thioflavin T and -S strongly stain amyloid deposits but are displaced from tangles by primulin. As stated in the specification, these findings demonstrate that these compounds may be used as blocking agents to saturate non-aggregated tau binding sites, but not as ligands of aggregated tau, since they do not disrupt PHFs and are not tau aggregation inhibitors.

Fourth, Friedhoff fails to teach or suggest the use of different sections of the brain, and specifically the medial temporal lobe of the brain, for studying neurological tangles. Instead, Friedhoff discloses the use of post-mortem whole brains. As stated above, whole brains are not diagnostic and cannot be used to determine Braak staging.

Fifth, Friedhoff fails to disclose or suggest a method that may be used for the detection of early Braak stages before appearance of clinical symptoms, pre-mortem diagnosis and discrimination of advanced Braak staging. Obviously, the use of a post-mortem brain precludes any pre-mortem assessment.

Sixth, Friedhoff reports the use of thioflavin dyes for a quantitative analysis of filament formation from tau protein in the presence of polyanions, specifically in the presence of polyglutamate and heparin (*see* pages 10228-10229). However, there is no evidence that either heparin or polyglutamate are indeed constituents of the PHFs isolated from AD brain tissues. Thus, it is questionable whether neurofibrillary tangles comprising polyglutamate and heparin are indeed true *in vitro* representatives of tau neurofibrillary tangles *in vivo*. Therefore, Friedhoff discloses simulated PHF-like *in vitro* tau co-assemblies, rather than real PHF *in vivo* assembly.

The Office Action recognizes the deficiencies of Friedhoff and acknowledges that Friedhoff fails to disclose methylene blue as a ligand that binds tau protein. Nevertheless, the Office Action relies on Wischik II for the disclosure of methylene blue and on Quay for the

teaching of benzothiazole-sulfonic acid compounds. Neither Wischik II nor Quay, however, remedy the deficiencies of Friedhoff.

Wischik II discloses an experimental *in vitro* tau-tau binding assay system to screen for potential inhibitors of tau protein aggregation and teaches that methylene blue blocks tau-tau binding (*see* page 11217). Wischik II, like Friedhoff, fails to teach or suggest a method for determining the *Braak stage* of neurofibrillary degeneration associated with a tauopathy in a patient. Wischik II only teaches that methylene blue can be used to dissolve PHFs and facilitate the proteolytic degradation of tau aggregates. Wischik II does not in any way address the problem of detecting or diagnosing Alzheimer's disease, let alone assessing Braak staging *in vivo* in a patient, using ligands that selectively bind to extracellular aggregated PHF tau in the medial temporal lobe of the brain. Furthermore, Wischik II fails to disclose or suggest a ligand, and specifically methylene blue, that is conjugated, chelated or associated with a detectable chemical group. Thus, Wischik II fails to disclose or suggest the claimed invention.

Quay discloses amyloid binding benzothiazole compounds that can be used as chemical markers. Amyloids are an amorphous mixture of protein, carbohydrate and lipids, that form neuritic plaques in the brain of subjects affected by AD, and thus are different in structure, function and processing from tau protein aggregates. Consequently, Quay, like Friedhoff and Wischik II, fails to teach or suggest a method for determining the *Braak stage* of neurofibrillary degeneration associated with a tauopathy in a patient.

B. There is no Reason to Combine the Known Elements in the Fashion Claimed

The obviousness rejection improperly selects isolated teachings from the cited references and combines them in an effort to draw conclusions regarding the claimed invention, when there is no logical motivation to do so. For example, the Office Action a) alleges that Friedhoff discloses thioflavin derivatives "as blocking ligands", b) maintains that Wischik II teaches that methylene blue has additional and separate advantages over the thioflavin derivatives disclosed

by Friedhoff, and c) infers from these alleged teachings that it would have been obvious to one of ordinary skill in the art to substitute the thioflavins disclosed by Friedhoff with methylene blue to label aggregated PHFs. The cited references, however, do not stand for such a proposition and the Office Action's allegations are wrong, because its characterization of the teachings of the cited references is factually erroneous.

Nowhere, in fact, does Friedhoff teach or suggest blocking ligands. The concept of blocking ligands to bind non-aggregated tau binding sites to enhance ligand binding for determining the *Braak stage* of neurofibrillary degeneration associated with a tauopathy in a patient is not envisioned at all in Friedhoff or in any of the cited references, for that matter. The Office Action's attempts to twist the teachings of Friedhoff to render obvious the claimed invention are unavailing. Friedhoff only discloses the use of thioflavins as dyes in a quantitative assay system to stain amyloid-like deposits and neurofibrillary tangles comprising polyglutamate and heparin in post-mortem brains *in vitro*. As stated above, thioflavine S and thioflavine-T are standard fluorescent stains commonly used in neuropathological studies of AD to bind amyloid protein deposits. Nowhere Friedhoff teaches or suggests blocking non-aggregated tau binding sites with thioflavin compounds. Thus, the Office Action's characterization of Friedhoff is factually inaccurate.

Furthermore, the Office Action, in its allegation of obviousness, presumes some motivation for wanting to specifically use conjugated, chelated or detectable chemical group-associated-methylene blue as ligand in preference to thioflavins, that finds no support in the cited prior art or in the knowledge regarding the different nature of thioflavins and phenothiazines.

First, Wischik II makes no mention of methylene blue which is conjugated, chelated or associated with a detectable chemical group.

Second, Wischik II clearly teaches that methylene blue, a phenothiazine, blocks tau-tau binding interaction and dissolves PHFs isolated from AD brain tissues. Thus, contrary to the

Office Action's assertion, there wouldn't be any logical motivation for the artisan skilled in the art to attempt to substitute thioflavin -S and -T in the quantitative assay of Friedhoff with phenothiazines, such as methylene blue, because phenothiazines that disrupt tau assemblies **could not** conceivably be used to monitor the formation of tau assemblies.

Third, the nature of the compounds in question proves wrong the motivation alleged by the Office Action. In fact, in contrast to phenothiazines, thioflavin-T and -S , which strongly stain amyloid deposits, are weak inhibitors of tau-tau binding (*see* Figure 10 in the specification). As such, the properties of thioflavins are antagonistic to the properties of phenothiazines. Therefore, the teachings of Friedhoff are of little relevance to the claimed invention, since thioflavins are strong β-amyloid ligands, but weak PHF ligands. Accordingly, contrary to the Office Action's assertions, the references provide no motivation to substitute thioflavin-T and -S with methylene blue as diagnostic for PHF assembly, because methylene blue blocks tau-tau binding interaction. The Office Action's alleged motivation is simply not found in the prior art.

The Office Action seems to confuse the concept of a ***ligand*** *which is conjugated, chelated or associated with a detectable chemical group, is capable of crossing the blood brain barrier and labels aggregated paired helical filament (PHF) tau protein in the medial temporal lobe,* with the concept of a ***blocking ligand*** that labels *competing non-aggregated tau binding sites in the medial temporal lobe and in the neocortical region of the brain.*

Ligands, such as phenothiazines, inhibit tau aggregation by binding within the aggregated repeat domain of the tau protein of the PHF core. Blocking ligands, such as sulphonated benzothiazole-like compounds, instead, saturate non-aggregated tau binding sites without inhibiting the binding of ligands to aggregated tau, and may be used to enhance the selectivity of PHF ligands for aggregated tau in the brain. Blocking ligands are strong β-amyloid ligands and, as stated in the specification (*see* paragraph [0015] in the published patent application), cannot be used for diagnostic purposes in determining neuropathological staging, because β-amyloid deposition does not discriminate between normal aging and Alzheimer's Disease.

Finally, the Office Action seems to imply that Quay, in disclosing benzothiazoles, renders obvious the use of thioflavin-T in the claimed invention. However, as stated above, Quay only discloses amyloid binding benzothiazole compounds that can be used as chemical markers to detect amyloid deposits and fails to disclose or suggest the use of ligands to detect PHF accumulation. As such, Quay fails to disclose a method to determine neuropathological Braak staging because β-amyloid deposition is not an indicator of Alzheimer's Disease.

In essence, the teachings of the cited prior art militate against any finding of any *prima facie* case of obviousness regarding the claimed invention.

For at least these reasons, the rejection under 35 U.S.C. § 103(a) is improper. Reconsideration and withdrawal of this ground of rejection is therefore respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed or rendered moot. Thus, the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date June 27, 2007

By [signature] 35,087 for

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5483
Facsimile: (202) 672-5399

Richard C. Peet
Attorney for Applicants
Registration No. 35,792